really is getting an exposure, on the average, ten times higher than the U.S. population. If we superimpose vaccines on top of that, if we're going to get any effect, we'll get it in the Seychelles as I mentioned. If we don't get an effect, I think it will be very reassuring for this situation.

As far as animal experiments are concerned, I understand that it's really not going to be practical to do a major Seychelles type study in this country with regard to vaccines, but I think that animal experiments are feasible. I mean, one can do a lot of neurobehavioral tests and kidney function tests on animals. There are three or four papers in the literature on ethylmercury, so we've got good guidelines to start with for ranging effects. So I would suggest we could do that or somebody could do that. We'd be happy to make them an offer. I'm in my elements this afternoon. I'm after research money.

The other point is that -- especially with regard to this figure here, the salicylic acid may be playing a role here. I've talked to some of my colleagues here

today and yesterday. We don't know how rapidly it may go from the intramuscular side. I've assumed in this figure here that it's a very rapid, almost instantaneous distribution, but it may not be and that's something we could test in animals, too. All our previous animal work has been done with ethylmercury chloride, which is a very lipid soluble commodity that diffuses readily from tissues. It will be interesting to see if the salicylate compound behaves the same way. For example, if you're looking at the transport of methylmercury into the brain, methylmercury-L sistine gets in the brain rapidly. The disomer, the optical isomer, the only difference is the optical activity. The disomer does not go into the brain. So the chemical compound, not just the mercury itself, but the chemical compound when mercury is present may play a very important role in its distribution and kinetics. This may -- If it was a slower release, for example, these peaks may not be as high as they are in this figure. So I think it's worth considering.

So with that, Madam Chairman, I hope I've earned myself a little grant of some sort. I don't know.

(LAUGHTER)

DR. RABINOVICH: Can I understand from your presentation that you think all of the -- answering all of these are doable?

DR. CLARKSON: Yes.

DR. RABINOVICH: Yes, thank you. Next, Dr. Michael Gerber.

DR. GERBER: Thank you. Well, as we've heard several times yesterday, as well as today, we can speculate on what the mercury levels may be in infants who've received immunizations with thimerosal-containing vaccines, but as far as the actual data demonstrating what those levels are, there really is very little. In fact, the only data that we have comes from stages of study at the nursery at Emory. We heard yesterday about the limitations of that study, the fact that it hasn't been published except in abstract form, the fact that there are only five term infants and fifteen premature infants, that the fifteen premature infants

had a mean weight of only 750 milligrams, concerns about the methodology of that study. So, needless to say, with that being the only data that we have, we really have very little.

As little as we have about the levels, we have even less about the distribution, about the kinetics, about the metabolism, about the excretion of ethylmercury. In fact, we know essentially nothing about those things in ethylmercury.

So what we at the NIH are proposing to do, and we're proposing to do this in conjunction with our colleagues, Dr. Ball and Dr. Pratt at the FDA, and we're proposing to do this through our vaccine and treatment evaluation units at Maryland and at Rochester, working with Dr. Clarkson at that same institution. What we're proposing to do is to attempt to obtain this data and we attempt to do this by getting together a cohort, first of all, of premature infants who have been vaccinated with the hepatitis B vaccine sometime within the last week to several months. These would be infants whose mothers were

hepatitis B surface-antigen positive, infants whose mothers hepatitis surface-antigen status was unknown, or infants who were born at hospitals that were not following the current recommendations of withholding the hepatitis B vaccine until a later time and those infants born to hepatitis B surface-antigen negative mothers.

And what we've proposed to do after identifying these premature infants is to obtain blood, stool, and urine specimens from them, as well as maternal hair samples. The maternal hair samples would be to get a baseline idea of what the in utero exposure had been. Maybe as a point of clarification, and we can get it from Dr. Clarkson later, I understood you to say that we could not measure inorganic mercury in hair, only organic, but I was unclear as to whether we could distinguish ethyl from methyl and maybe you could address that later.

But, in any case, in addition to the premature infants, we would then want to look at a cohort of term infants and look at term infants coming from three different

kinds of pediatric practices, one practice in which the routine immunization had been providing the patients with vaccines that had a relatively high amount of thimerosal. We would want to look at a second group of practices where the cumulative exposure from vaccination of thimerosal would be relatively low, and then, finally, practices or a group of practices where only thimerosal-free vaccines had been used. Again, we would want to look at these infants within one month to several months following the two-month immunization and at that point determine what the exposure, what the combined exposure had been at that two-month visit, as well as all of the possible previous exposure to thimerosal from earlier immunizations, and collect blood, stool, urine from those patients, as well as maternal hair samples if we could.

We would also want to look at a similar group of infants from those same three types of pediatric practices after the sixth-month immunization and, again, make a determination of the total thimerosal exposure at that six-month immunization, as well as any

exposure from previous immunizations and again collect blood, stool, urine specimens from those infants, as well as maternal hair samples if we could. Hopefully, with that information, we would be in a position to make some determinations about what the expected mercury levels would be after immunization with thimerosal-containing vaccines, about what the distribution, what the metabolism, what the excretion of ethylmercury in these infants would be.

Is this feasible? I think it is feasible. One limitation of the feasibility is trying to do this as soon as possible while children are still receiving thimerosal-containing vaccines. Why is this important? If we're moving towards -- hopefully moving towards a situation where infants in this country would no longer be receiving thimerosal-containing vaccines, I think there are three reasons. First of all, I think the information that would be obtained would be helpful for those parents whose infants have already or will continue to receive thimerosal-containing vaccines.

Number two, as we heard from Dr. Clements, although we

may be approaching thimerosal-free vaccines in the near future, for much of the world, this is something that's not going to happen for several years, at least several years, so this information would be important for those populations. Finally, as one of the charges in the Joint Statement from the American Academy of Pediatrics and the Public Health Service, this type of research was one of the things that we had committed ourselves to performing.

Thank you.

DR. RABINOVICH: Alison Mawle.

MS. MAWLE: When Gina charged the individual panel members, she deliberately did not want us to consult. So if some of the same things came up, you would presumably take it as a reinforcement of the kind of things we should be doing.

I think speaking -- I work at CDC. I'm part of the National Centers for Infectious Diseases, and as we have listened over the past two days, but also over the last several weeks, to some of the issues that have been brought up around thimerosal, I have been

repeatedly struck by the fact that we really don't know how this compound breaks down. We heard yesterday from Jeffrey Englhardt that there's very little kinetic data on thimerosal, but the one paper that we have seen in squirrel monkeys suggests that a fair proportion of this breaks down not into ethylmercury but breaks down into inorganic mercury. And we've heard the data on methylmercury. We're now hearing a little bit about how we want to do the studies on ethylmercury. I think it's absolutely critical that we know how this compound breaks down, because if what we're looking at is inorganic mercury, we're looking at a different thing again. We've heard very little at all about inorganic mercury. Dr. Clarkson mentioned that if we want to do studies in hair that we cannot use inorganic mercury as a marker. I have learned more about how you do these studies over the last few weeks than I ever wanted to know and I still feel very ignorant about many of these things, but I do see that -- do feel that that is, in terms of both feasibility and urgency, one of the first things we should be doing. It's, certainly in animals,

a fairly straightforward experiment to do.
Other speakers have talked about looking at where it's compartmentalized, the issue of giving thimerosal intramuscularly versus orally, which is where most of the data we have on methylmercury comes from, what is the half-life, is it excreted in infants -- I was very surprised to discover that it's thought there is no excretion, but we don't know -- the role of the bolus effect. I'm also delighted to hear that you're going to be going back and looking in the Seychelles at the possibly effects of immunizations. I don't know --
DR. CLARKSON: Why don't you come? It's a nice island.
MS. MAWLE: I'd be delighted to come. I just don't eat the seafood.
But I think that that's a real important study to do, clearly from the Faroe Island studies and the Seychelles Island studies. If there are effects of the mercury from the vaccines, they're going to be subtle. It's going to be very hard to do any kind of study in current populations that are being immunized, especially as we have heard from FDA that the

commitment is to move towards mercury-free vaccines if at all possible. I think that -- I've certainly not heard any argument against that. If we need preservatives in certain cases, if we need to keep thimerosal there for a specific reason, FDA will be willing to discuss that, but, clearly, the move is to move -- get rid of mercury if we can. That comes in the context of the environmental mercury load. I think it's very easy for us to focus on our little issue of vaccines, but that's not where this is coming from. This is coming from the fact that we live in a mercury-contaminated environment and seeing the contribution of vaccines within that context I think is critical. From CDC's perspective, I think it's very important and very urgent that we monitor any changes on immunization practices. The data that Eric Mast presented yesterday I found very disturbing, that in such a short time you can already see an effect of this. We heard from -- I don't know if they're going to address this, but we've heard from the manufacturers over the last few weeks that we could not go to a thimerosal-free schedule

right now without introducing dramatic vaccine shortages, which would totally disrupt the current schedule.

So we clearly want to keep our current immunization program in place, we want to reassure people, and we also want to -- in some way, come up with a time line for reducing or removing thimerosal. I think that that is something that CDC can contribute to in terms of doing surveillance on what effect is being had on the schedule itself.

I don't want to talk much about the manufacturing issue, but I did hear the issue of combination vaccines raised. I think that -- I mean, there were many other compelling reasons for going towards combination vaccines, but I think that that is something that we should be pushing towards, but if we do need to be keeping preservatives in, then, obviously, that's a way of reducing it. Looking at other ways of reducing the thimerosal load, we heard the idea of reducing the amount of vaccine that's actually given.

Lastly, I just want to leave you with the idea that we

really, really need to increase our ability to communicate with our constituents. I think that we can certainly be faulted over -- in terms of being complacent about the efficacy and safety of vaccines, and it's become clear over the last two or three years that the public's concern about vaccine safety has risen. We've seen congressional hearings recently on that issue, and I think the way that we communicate, both with the public and also with providers, is critical in terms of maintaining confidence in our program and in giving them information to give to their constituents in order to reassure them, or not, if that's what we need to be doing as we've seen in the case of the rotavirus issue, which has been going along parallel with that.

So I hope that's given a few thoughts from our perspective. Thank you.

DR. RABINOVICH: Dr. Paradiso, Wyeth-Lederle.

DR. PARADISO: Thank you, Gina. Gina said I only have a half-an-hour to talk, so I'll try to go quickly. I have to first apologize for the fact that I was not

here yesterday. I couldn't make it, so I missed a lot of the detailed discussion. I want to tell you that during the course of the several weeks and also during the course of this morning, when thinking about research in this area, particularly as it relates to thimerosal and what we need to know and what we don't know, I have a little trouble getting past the fact -- getting past what we're going to do with any data at this point that we collect with thimerosal. I think that we have made a judgement -- or a judgement has been made on the basis of a desire to eliminate thimerosal because it makes sense not to inject mercury. And there is not, to my knowledge, a specific outcome besides that that we're trying to avoid. So in designing studies to look at thimerosal, it's hard for me to think specifically about outcomes that I would have any confidence in or that I would think about to counterbalance the decisions that have been made so far. I'm not trying to be flip about this, but I think -- I think we have to be a little careful about thinking that data that we collect on thimerosal, while

I think it will be useful in our understanding of thimerosal and its metabolism, it's not clear to me that it's going to tell us too much about potential rare adverse events that may occur as a result of having thimerosal.

Now, having said that, at the end of this morning, I heard Dr. Clarkson, who knows far more about thimerosal and mercury than I do and also is from Rochester like I am, so that raises him a little bit higher on the scale -- Rochester, New York, that is -- it seems clear to me that we, infectious disease vaccinologists, perhaps have no idea how to use these numbers that we're using and using as our guidelines. So if I were to back off what I said at first and think about things that I would like to know, it would be: How do we assess cumulative effect when we talk about vaccination? The only data, I guess, that would be convincing to me would be data that actually measured levels in the blood or in an appropriate bodily fluid that could be related to the potential toxic effects that we're worried about. Those are mostly neurological. You

know, I think we need to, however, then think, what if it's undetectable? Would that change what we're thinking? If it wouldn't, then we have to accept that the outcome of these studies is going to be for our understanding and not going to really help us in terms of future use of thimerosal.

So I think we, as manufacturers -- or our company is looking more towards potential new formulations or new preservatives that could be used or towards the elimination of the use of preservatives, and that obviously gets us to single-dose vials. I think it's important for us not to underestimate the practices that was just mentioned in the United States. Multi-dose vials are greatly favored. I mean, the reason we use them in the United States is because that's what the physicians' offices prefer. In Europe, that's not the case. They, in fact, prefer single-dose vials. So that is the market there.

So this is not an overnight change from a multi-dose dose presentation to single-dose only because of the capacities that have been developed in our

manufacturing around those needs.

In thinking about new preservatives, I think we need to think hard about what outcomes we'd be looking for from a safety perspective when we use new preservatives, and it seems clear to me that tests for toxicity that thimerosal passed are obviously not enough for the next preservative. So we need to think about what outcomes we're specifically looking for. Somebody said this morning, for the unknown, the new preservatives are really the unknown and without experience, and we need to think in our research, when we think about research, what those outcomes would be.

Lastly, I just want to comment, Norman Baylor talked this morning about the FDA review process and the desire to expedite review. I need to point out that on those two slides, the list of potential requirements for the presentation for a new preservative or the presentation of any new formulation is potentially not a small task, and if you're talking about doing stability studies in real-time, usually that's a two-year real-time stability study. If you're talking

about doing consistency studies and if you're talking about efficacy trials, you're talking about several years and fairly major programs for the presentation of new preservatives. So all of that needs to be put together before the review process can start, obviously.

So I just wanted to tell you that when we think about these changes in formulations, we think about the time lines that are required prior to that submission and those are fairly long time lines from a manufacturing perspective.

That's all I've got to say. Thanks.

DR. RABINOVICH: Dr. John Risher?

DR. RISHER: This will be a little bit of a challenge for me. I teach biology classes for six hours on Saturday and I always run out of time before I get the information through. So five minutes is really going to be a challenge.

Most of what I have to say, and I'm approaching from a toxicology and human health risk assessment perspective, has already been said, but I just wanted

to put a couple of points of clarification that I don't know -- This may help. This is just from a general introductory biology textbook. I don't know how many people really understand when we're talking about the main specific effects versus global effects. An example of the global effect is IQ. The main specific effects -- This is 1999, so we know a lot more about the brain than we did a hundred years ago and we know that specific areas of the brain are associated with specific cognitive or motor functions. I don't have a pointer here -- Oh, great, thanks.

If you can just look, where it says "language structure" on the upper left and go down, we know that certain areas of the brain are associated with that. So specific neuropsychological tests are designed to probe specific cognitive functions and the ultimate intent is to find out if -- even although you may not have been exposed to enough of a substance to have an effect on global function cognitively, there still might be enough effect in a particular area of the brain associated with a certain function. So when they

talk about domain-specific effects versus global effects, that's, in general, the difference between the two.

Again, the first one on here is just common sense, but what I did is I tried to break down things that I thought might help from a risk assessment perspective. The first is really more of a common sense thing and it could easily be an in vitro study if it has not already been done. This is just to look at the effectiveness as a preservative of reduced amounts of Thimerosal. Again, that would -- if it has not already been done by the manufacturers, it'd be an easy thing to do.

Metabolic and biomarker studies are also important. Again, these have pretty much been covered, but we know that Thimerosal is actually water-soluble. So as a water-soluble substance, it's possible that it could be excreted through the kidneys as Thimerosal. So how rapidly is that bond between the group, the sulfur, and the ethylmercury broken? If it's not broken quickly, then there may not be the level of exposure

theoretically that there would be as if it were quickly broken.

Then, of course, we've already discussed the measurement of both ethylmercury and mercuric ion in the feces and urine. Having had three kids, I'm glad I'm not going to be a part of having to dip into that one.

Ethylmercury in the hair of the Seychelles Island population -- Well, the Faroe I'm not sure about. Dr. Grandjaun is not here, but Dr. Clarkson has already addressed the ethylmercury in the Seychelles population. So they might look into that.

Another thing regards one of the differences in looking at this Thimerosal is not only the fact that it's a bolus, we're talking about most of our knowledge relating to either the unborn or to adults, and I just want to really quickly explain something and then suggest that it might be looked into.

In adults, the primary source of excretion of organic mercury -- Primarily methylmercury is what most of the information about -- is through an enterohepatic

circulation. That is that the mercury is absorbed from the gut and it goes up through the circulation into the liver where it's conjugated with glutathion and leaves the liver in the bile salts back down to the gallbladder, through the bowel, and then back into the intestine where it continually gets recycled. So it's not always bowel available. Now, in rodents we know that during the suckling period, which is about twenty-one days in rats, that the glutathion, which is needed to conjugate the mercury, is not produced in sufficient quantities to lead to the circulation. There's been some studies in primates that have shown that in real young primates that that might also be the case. In humans, we really don't know, it may be the case or it may not be, but I think it would be interesting to find out when that enterohepatic circulation is to the extent that glutathion is produced and can conjugate the mercury and actually comes into being. That ties into again with excretion.

Longer-term things: A lot of classic toxicology-type studies; neurodevelopmental studies of Thimerosal which

would do dose-response studies and research animals and also look at different ages of animals, particularly after the animal is born and how the early stages of development compares to adulthood; the next one, contribution of Thimerosal from vaccines to total and individual tissue burdens. Kate Mchaffey from EPA and others were stressing the importance of looking at the total body burden of mercury. We're not just being exposed to Thimerosal. We're getting some in our food and some from other sources. ATSDR is involved in a Great Lakes research project that it's been sponsoring for years or co-sponsoring, and we may have some of this data and this may -- we may have the mechanism for getting some of this data.

The last thing is the immunologic effects of Thimerosal need to be investigated in laboratory animals as well. I'm sure that's five minutes plus.

DR. RABINOVICH: And last is Dr. Bernard Schwetz.

DR. SCHWETZ: Thank you. It's always fun to be the last of a series of speakers who, for the most part, vigorously agree with each other. It's very hard to

say something that's new and unique. On the other hand, I want to offer some thoughts as the Senior Science Advisor to the Commissioner of the FDA and the Director of the FDA National Center for Toxicological Research.

As you might expect within an organization of the nature and size of the FDA, there will be different research agendas on almost everything, and that certainly would be true for ethylmercury as well, but a point I want to make is that I think that because of the nature of the exposures, these converge for something like ethylmercury.

If Thimerosal or mercury is taken out of vaccines, I think further work on ethylmercury for the Center for Biologics would not be a very high priority, especially in comparison to the need for data on the replacements for Thimerosal. I think this isn't just a question of a research agenda for ethylmercury, it's an even more important question that if we succeed, then the problem starts of knowing how successful the replacements are. That has got to be a high priority, along with

whatever we need to know about ethylmercury.
On the other hand, it isn't very likely that Thimerosal is going to be replaced in vaccines completely in a reasonable length of time. So that is still a need to have data on ethylmercury. Then look at the bigger picture of the FDA in total where the concern is for drugs, cosmetics, foods, as well as vaccines. Then it's a given that we need to have more data on ethylmercury to understand that kind of a complex picture. It must include considerations about additivity of ethylmercury from different sources, but a point that hasn't been made in this meeting so far is the need to consider the additivity between ethylmercury and methylmercury. We treat them as if they're not acting in the same cells, and at some times they are. So I don't think we can look at ethylmercury in isolation without considering methylmercury or other sources of ethylmercury other than vaccines.
So one of the high priorities that I think is for us to reduce the uncertainties that surround the idea that methylmercury and ethylmercury are the same. We know

they're not, but that's where we are today and we don't have much data on ethylmercury to really confirm whether it's more or less toxic. We know for the kidney it's probably more, but we all seem to assume that methylmercury is the gold standard for concern and ethylmercury may not be as bad. We don't have enough data to say that with a hundred percent confidence. While there are some priorities that I would say maybe just a little bit differently than some of the preceding speakers, I would agree that the sensitivity of the fetus versus the neonate is very important, and for some of you who have forgotten about the sensitive windows during fetal development, the nervous system develops post-natally. So isn't unreasonable to expect there would be particular windows of sensitivity. So it isn't the matter of averaging the dose over the whole neonatal period, it's what's the week or what's the day or what's the series of hours that represent a particular event in the development of the nervous system when this whole thing might be dangerous. It may be weeks surrounding that when there isn't a major

problem. We don't have that information.
The idea of sensitive subpopulations, as I reviewed literature on ethylmercury, it appeared as though there were people who were much more sensitive than others -- This is adults, and I don't know why, but the possibility that that would exist with neonates is not impossible -- the question of peak blood levels versus the blood levels -- I distinguish between a single exposure and chronic, because when you're talking about newborns, that's not chronic. That's what happens right then and the following days over which they're not exposed to a vaccine again.
So the real question in my mind is the peak -- the effect of the peak blood level versus the blood level during the distribution and elimination phase of the original exposure to ethylmercury. Then you add to it another exposure beyond that with another vaccination or from food or whatever, but it isn't a matter of chronic versus acute exposure for this neonate. We don't know the impact of the area under the curve during the elimination phase versus the impact on the

cells of nervous system during that peak level. Is it just a difference in the exposure? Is that just the dose response curve? Or is time important? That, again, gets into the windows of sensitivity and we don't have the kind of data to address that.

In addition, the intermittent versus the continuous exposure, there are examples where intermittent exposure is important because the rate of delivery to the cells is more important. The rate of delivery, the rate of change within cells, could be more important than the average concentration. That could explain the intermittent versus the continuous response.

The valid bar markers of exposure, I think we have to have that. That is obviously of considerable importance. The elimination from the neonate, we're using a conservative estimate when we say it's not being removed by anything other than dilution, but we need to get that information.

One that I haven't heard discussed, the fact that we know that ethylmercury is a skin sensitizer when it's put on the skin and now we're injecting this IM at a

time when the immune system is just developing, the functionality of the immune system is just being set at this age. So now we're injecting a sensitizer several times. During that period of time, what's the impact of a sensitizer -- of something that is known to be a skin sensitizer, what is the effect on the functional development of the immune system when you give a chemical of that kind repeatedly IM?

Now, regarding the question of feasibility and urgency, the kinds of studies that we're talking about, the pharmacokinetic studies, the distribution, the elimination, all these other things that we can do in rodents, we can do them in primates, so those are feasible. It just takes money and expertise and good work. We don't know need shotty work at this stage by people rushing in and doing something that they don't quite know what they're doing. This is a time when the rest of the data that we make new decisions on have got to be better than the quality of information that is normally available when people on a random basis begin to collect information and, in retrospect, it doesn't

fit into a real good picture when you analyze it. That's true of a lot of chemicals. There need to be some definitive studies now that are done very well. The urgency, from the standpoint of -- Now I'm speaking as a toxicologist. I think anytime there's an avoidable source of exposure to mercury, we need to look at it real hard, but, obviously, there are consequences in many cases of taking steps. I don't think this is an emergency, that mercury is being used in this manner, but if it's an avoidable exposure, we should do something about it. I also recognize that if we do something precipitous, we could create an emergency and that has got to be considered as equally important as the concern over mercury itself.

Why mercury represents a priority concern for me as a teratologist and a developmental toxicologist who has been doing this kind of work my whole career is the fact that this can cause irreversible damage to the development of the nervous system. That's why, in my mind, it's different than nephrotoxicity. A reversible damage, whether it's in an adult or a neonate,

whatever, that's different than permanent damage to the function of the nervous system, permanent damage to the function of the immune system. So that's why I think, among the issues that we look at with mercury or with other heavy metals, the fact that you would cause irreversible damage to the nervous system, in particular, is something that makes the kind of priority where we shouldn't sit back and say, well, we got through this one and now we'll pay attention to other priorities. I think we've got to stay on mercury.

Thank you.

DR. RABINOVICH: Thank you. With that, I'd like to ask all the panel members to come up to the front table and I'd like to open the floor for discussion, and I see that they're lined up already. So you guys better hurry up.

Dr. Klein?

DR. KLEIN: Dr. Clarkson, I'd like you to amplify your remarks, particularly in regard to that graph that you showed, the figure, in terms of a potential first dose

of vaccine that has thimerosal in it given at birth. Now, you indicated that your -- that it would be about 4 micrograms with that first dose. I wonder if you could -- If you eliminate that first dose, the rest of the curve presumably would be approximately the same; is that correct? In other words, what benefit do we gain in your model from eliminating that first dose?

DR. CLARKSON: Not a lot. I guess you've seen this before, but this basically -- As we said, all of these guidelines that we've talked about today don't start with the dose. Well, some of our Iraqi stuff did, but, basically, when you're making these risk assessments on human health, epidemiologists -- (inaudible) on ethylmercury, you start with a hair level or blood level, let's say a minimum toxic level or some threshold level, some level associated with toxicity. Then an expert committee may or may not apply safety factors. For example, originally, from the Japanese data, there was a blood level of 200 parts per billion. A committee comes along and applies a safety factor of 10, so it's now 20 parts per billion in blood. Then

from that point, the committee will go on and figure out -- calculate what is the long-term daily dose that will give you a toxic level of 20. That's how it's done. There's various calculations.

The original data is not a dose. It's a blood level or a hair level. And the best way for us to compare a single dose to the chronic dose is to ask blood level results from that single dose or what blood level results from that chronic dose. The example I mentioned this morning with eating six ounces tuna fish, which has something like 17 micrograms of mercury -- Let's say 20. Well, if you consume one can, the effect on your blood level would be so tiny you can't measure it, but if that's taken day after day after day for six months to a year -- It takes about a year to get into a steady state where intake balances excretion -- that blood level will rise measurably to a level of about 20 parts per billion, which is one of the FDA safe limits.

So a single dose is a very different situation than a chronic dose in terms of body burden.

Now, in this case, you go to the top, a single dose of 12.5 micrograms here at birth, given the bodyweight -- We took a bodyweight of 1.8 kilograms -- and we assume the blood volume was 8.5 percent bodyweight and you assume that

5 -- You do all this arithmetic and you will come out with a blood level of about 4 parts per billion, which is about where the equivalent blood level will be for the EPA guidelines. So you get with this one dose to about the EPA guideline. You certainly do not exceed, as I heard this morning, by a factor of 10. Okay?

As you continue with these doses over this six-month period, assuming there's no elimination of ethylmercury from the body and assuming ethyl behaves like methyl, you will -- eventually, you will exceed the EPA guideline. At month number 2, you will get up to a level of about 15. By six months, you may get up to a level in the 20s, which then starts to exceed the other guidelines, the FDA guidelines, the ASTDR, and so on.

DR. KLEIN: I'd like you to superimpose on this curve. Let's say there is no vaccine given at birth, but the

same series of immunizations is given beginning at two months of age. Does that affect your curve at all?

DR. CLARKSON: Well, it would reduce every one of these points by about 4 parts per billion. Essentially, what would happen is you would have a line sort of parallel to this, which would start off -- Usually, background levels in blood are less than 1 part per billion depending on how much fish the mother may have consumed. So you would just draw a line more or less parallel to this with 4 parts per billion below it. So you would still get in six months, you know, close to about 20 parts per billion, close to the other guidelines.

DR. RABINOVICH: Thank you. Next question? Dr. Orenstein?

DR. ORENSTEIN: I was interested -- I guess I did -- Walt Orenstein, CDC.

It's interesting that I didn't hear anybody talking about looking at outcome kinds of studies in vaccinated children. Roger Bernier presented data from the Vaccine -- one of the institutions in the Vaccine

Safety data link. Kaiser I think had over 30,000 children in a distribution at least of different thimerosal intakes, and I presume most of those kids are now between two and four years of age or somewhere along that line.

Is there a reason why none of you considered that? Or is it I didn't hear you? Is it too many confounders, too difficult a study to do, or do you think it would be worthwhile trying to look at some outcome in a population such as that?

DR. RABINOVICH: Dr. Gerber?

DR. GERBER: Maybe one of the people who's been actually involved in the Seychelles or Faroe studies can comment on this, but my impression is that those studies were extremely difficult to do in those limited, very limited populations compared to the United States, and that to attempt to reproduce something like the Seychelles studies or the Faroe studies in this country with all the potential confounders would be -- the expense would probably be prohibitive and it would be extremely difficult to do

properly.

DR. RABINOVICH: Dr. Clarkson, do you have any comments based on the Seychelles experience?

DR. CLARKSON: Well, I agree. The number of covariants that we have to take into account in the Seychelles is really quite large anyway, and I imagine it will be much worse here. You can't do a randomized clinical trial, but that would be the ideal scientific way of dealing with it.

DR. RABINOVICH: Dr. Schwartz?

DR. SCHWARTZ: One of the things that I think we need to consider is, as a couple of the speakers have said, that the cat is out of the bag, the horse out of the barn, and that thimerosal is going to be out of the vaccines. In addition not only to looking at the replacement for thimerosal, which I think is very important, and the gentleman who spoke earlier from SmithKline didn't specify exactly what has been looked at with 2-phenoxyethanol, and I think we need to make sure that our potential concerns with that substance and with other substances are dealt with.

One of the other things that we haven't looked at is what other additives there are in vaccines or adjuvants that are used with vaccines and what the impact of those may be. I think if we're going to learn anything, it is that thimerosal has been in vaccines for a long time and nobody really thought a whole lot about it until all of a sudden it seemed to spring on everyone's consciousness, and there may very well be other things that are parts of the immunization program that are found in vaccines and we need to do, I think, a much better job thinking about what additional research may be done in order to be ready should any concerns arise in the future or to identify any problems before they're identified by the media or people who may misinterpret what those data mean. I think before I spent any money doing further research on thimerosal, I would be inclined to look very carefully and see what money needs to be spent on things that are going to be important to the vaccination program in the U.S. in the future.

DR. RABINOVICH: Yes, please, Peter?

DR. PARADISO: I think it's a misconception, at least to me, that the thimerosal issue or that the concerns about thimerosal were sprung on anybody. I mean, we -- At least on the vaccine manufacturer side, this is an issue we've been dealing with for quite a number of years. And in Europe, we heard this morning, it's been a fairly major issue for a number of years, and we have been moving in the direction that in new vaccines in the future is actually to move away from the use of thimerosal because of -- because of the concerns and the potential unknowns about it.

So I think it's unfair to say that this was a surprise, that we, from a manufacturing perspective anyway, didn't know about the issues with thimerosal. I think the surprise was more the reaction to it and the immediacy in the U.S. particularly.

So I want to add to that to say that there is generally very great care taken to what is put into vaccines and the potential toxicity of what is put into vaccines. Perhaps, we can see that the most when we think about adjuvants and new technologies for improving immune

responses. That has been a process that we've been working on for probably the last ten years and it is a slow and careful process guided by toxicology and guided by our desire to make sure that we don't introduce anything that's not safe. So, you know, I think we are doing that.

DR. RABINOVICH: Dr. Zoon?

DR. ZOON: Yes, Dr. Zoon, CBER.

A point I would like to just mention, while I agree that we need to look at the future with respect to other potential preservatives, I do think we're looking at a transition period where even -- a very long transition period where thimerosal will continue to be used in a number of vaccines. So I probably share less -- I feel like the balance needs to be looked at on both ends. What are the risk factors and what is the information we need to know to make good scientific decisions and guidance with respect to the use of thimerosal and really understand that so that we can give good instructions and good advice. But as we heard, if we, if ever, go to zero, we need to still

deal with those issues.

So my sense is that we need to achieve a balance here. We need to understand more about thimerosal because in the past two days, I think we have recognized there really is a paucity of data and I think some of the points made about looking at the developing nervous system, looking at the developing immune systems and the effects of these agents on that at critical times of development hasn't been -- hasn't been done, and I think that knowledge is very important.

So I would -- While I agree with some of the comments that we need to look to the future, I also think there's a lot of science that need to be done in looking at these organomercurials.

DR. RABINOVICH: Dr. Halsey?

DR. HALSEY: I just want to respond to Walt Orenstein's question and I would have said it anyway, but I think there is a problem of perception. I personally think it's very unlikely that any harm has been done. I don't think anybody believes -- most people don't believe that it has. I really -- I don't think so.

But I think the public perception will be that it might have, and we know from our experiences that we've been dealing with in the past five years with regard to alleged adverse events of a variety of type, that including things that we have learned some of the subtle neurologic defects that may come from the studies in the Faroe Islands, you can bet there will be many parents who believe their child may be affected. And they do need data to address that issue. I believe the data will be likely to be negative, but if we don't have the data, how can we say that it's not negative? This is one situation where there will have been exposure to something that might have done it. It's not the same as some of the other allegations that we have dealt with.

So I do believe that there is a need and probably for much more than the study that Walt was talking about, which is a limited number of small -- a relatively small number, even though it's in the tens of thousands of children, to just take a look at some of the simple outcomes, but there probably is a need for a careful

study. I'm not that type of investigator, but the people who do these neurodevelopmental things very carefully need to determine the feasibility. They need to look at all of the other exposures. This is not a simple study. This would be very complicated and I don't look forward to being responsible for those, but I think if we don't have that, we're just going to have the continued public trust erosion that says you don't care or you don't think so. And what's going to happen to the Vaccine Compensation Program? There will be, undoubtedly, applications for that and who knows what's going to be the outcome of those deliberations by the Special Master.

So I think there is a need and probably for more than one study based upon the problems that we've seen elsewhere by the interpretation of different studies and in different populations who have a very different baseline rate of exposure to mercury. You can't just pick those populations that are at the low background of other environmental exposure because you're likely -- you're then -- it'll be stated, perhaps correctly,

that you biased it in your favor in saying that there's no effect from those.

DR. RABINOVICH: Comments from the panel or from anybody in terms of need for such a study?

DR. MAWLE: I wouldn't disagree with you, but in terms of public trust, it's an important question to ask. I feel quite strongly that we have -- there's a lot of data that we need to know just about what happens to the thimerosal before we can even get into those studies. So I think it's something to bear in mind. I was very happy to hear that Dr. Clarkson will be able to look or possibly be able to look at what happens to vaccines in the Seychelle where there is a huge burden of mercury. If that's possible to do in the Faroe Islands, I would want to do it there, too, where you already have the careful outcome measures looked at. I agree it's not the U.S. population, but it would certainly give you a parameter and a range for where you can start to apply that to this population and to get an idea of whether we really need to do them. The biggest problem I have with that is that if we find a

negative, then there will be so many confounders that people will say "Well, you just didn't do the study right." And for the time and expense, I would say that that was -- that's the kind of study that you want to keep in the back of your mind, and Gina talked about looking for populations, databases that may have been collected for other things that we could possibly get that kind of data from that wouldn't involve setting a study de novo.

UNIDENTIFIED SPEAKER: Bill (inaudible) from Wyeth. I have sort of similar comment maybe since you said exactly what I was going to say. My question is actually for Neal which is that, since you seem to think there is a clear and present sort of danger here that should be taken out immediately, what data would you need personally to be convinced otherwise?

DR. HALSEY: Let me clarify, I do not think that there is evidence of a clear and present danger. That was not my intent by anything that I have said, but I have participated in writing in the Academy statement and elsewhere that there is no evidence that harm has been

done. There is a clear problem with regard to the potential or the perceived potential for harm, and I believe that the correct steps have been taken by the FDA at this time of requesting within the realm of what they're capable of in the absence of any data of requesting action to determine what can be done and how fast it can done to remove this.

So the corrective step from that standpoint has been taken. What I do believe has not been done adequately to date is a showing of the uncertainties that we have at this time and provision of more specific guidance to physicians with regard to what options are available. I mean, the basic principles that I learned a long time ago about dealing with perceived risks is that you do take an action, but you also have to inform people of what additional steps they may take and this is not too different than some other vaccine safety issues that we've dealt with in the past five years. We have DTP whole cell and DTaP, the acellular pertussis. We have given a preference to that vaccine that we think is safer with regard to some side effects. With regard to

inactivated polio vaccine versus oral polio vaccine, we have moved in a fairly rapid process toward the vaccine that seems to be safer, but one of the first steps we did was to inform people that there were two different vaccines and that there are these benefits and risks of each one. We haven't taken that step yet with this process, but I think we have an obligation to physicians and the public to at least talk about the actions that are there.

DR. RABINOVICH: I guess I'd like to comment having heard part of the process. The web pages have had for a long time the concern about thimerosal and that we're giving children mercury. Those have been up for a long time. My groups have known that vaccines contained mercury. What was new then and sort of gave rise to the urgency was not knowledge that it was mercury or mercury-derivative, but the content, the volume. And I think it was the assessment of the potential highest exposure given the immunization schedule and the products available.

You raised questions about communicating uncertainty

and at what point you send that out further. Bruce, you've been dealing with this for a year. Maybe there are other experts here on risk communication. How do you take something which has been out in the community, it's on the web pages, where we have a little bit more information which give rise to concern and which our vaccine information statements already contain everything from hypersensitivity to death on every single statement -- how do you more appropriately answer concerns? Can you comment upon that?

DR. GELLER: Well, if somebody has the answer to your question, they should be speaking and not me.

But I will say that one of the things that we've heard, and I think that while this session is designed to sort of sketch out a potential research agenda which people can go back and figure out what's feasible and not, what's fundable and not -- One of the things that we heard at the hearing and that we hear repeatedly and I think Neal echoed in some of his comments just a minute ago was the sense that you need to actually demonstrate that you're taking these concerns seriously and doing

something about them. I think the fact that we have recommendations for vaccines and people have a perception that they've been harmed in some way and nobody cares about harm is really a big part of the problem. So I think that as these various studies get sketched out, I think we all need to know what they are. So that when someone -- when people ask us, they say, "Well, what are you doing about it?" that we can be very clear about all that's going about it. There's a lot going on already. We've highlighted a number of things that are deficit, but I think we also have to be clear that all of this is going on because, though this is the information age, we'll never have complete information. We're always going to live in some sort of uncertainty and I'm sure that nobody would have ever dreamt that this would have been the issue of the day and now we see all the gaps in this. So I think as we begin to move along, there will be other things like that and we always recognize that there are more things to fill in, and I think what we're doing about those is something that we have to communicate quite vigorously.

DR. RABINOVICH: Plotkin?

DR. PLOTKIN: Well, as this meeting draws to a close, I am -- we're talking about perceptions, perceptions of danger and so on, I must say that I'm reminded of Alice in Wonderland. Now, I don't happen to remember the exact story, but at one stage I think Alice is talking about a situation and she says, "Well, we'll have a trial and then we'll have a sentence." And the Red Queen says, "No, first the sentence and then the trial."

So, you know, it strikes me that a perception has certainly been created through the change in the vaccine schedule and so on and that there is a real problem. Now, after these two days, I must say that I'm actually less sure that there is a problem while I was when this meeting started. I do have to repeat my comment that I think this meeting should have been held sometime ago before the announcements.

DR. RABINOVICH: I think that's a point well-taken. I'd like to thank the panel and turn it back to Dr. Marty Myers.

DR. MYERS: Dr. Modlin had to leave to make a plane just a little bit ago and asked me if I would take over at this point and ask Dr. Klein, our rapateur, to give us a summary. We're a little bit ahead, though we seem to be at that point. Dr. Klein?

DR. KLEIN: My job has been made easier by this afternoon's discussion. I think it was the best summary of this meeting. It included almost everything that I had noted. So I will touch on only a few points.

One, the goals of the meeting were to inform and have dialogue among experts from different disciplines, and I think we've achieved that very successfully. Certainly, for those of us whose knowledge of ethyl, methyl, or other forms of mercury was limited or none, we've learned a lot. I think we'll all be able to find the Seychelles and Faroe Islands on the map and be able to discuss them with authority.

(LAUGHTER)

DR. KLEIN: Dr. Myers and I will develop a summary that will be published in MMWR. We'll have to call on some

of you to clarify and make sure that we don't write something that is either unintelligible or incorrect. So we'll be calling on you for your help.

I think we've learned that preservatives are critical in the preparation of vaccines and there will be preservatives, even if they are different from the ones that are currently used, but they are important during the manufacturer process, during administration, and particularly during multi-dose vial usage. Even there, the concerns that the multi-dose vials be used as instructed on the label and that they have a relative limited period of time for their usage and the contamination may overwhelm the preservative if those instructions are not followed.

In relationship to the manufacturer processing, I was particularly impressed with Dr. Clements' discussion and presentation that there are a lot of manufacturers in countries with different standards and that perhaps some of the data that will come from these areas of research will be universally available for local manufacturers and perhaps give them an additional

safeguard.

The regulation issues, I raise a question of timing in the sense that any new product or change in formulation is substantial in terms of new studies that will be needed and this is a process that will be gradual and take place over a period of years. Dr. Clements gave the timetable. Dr. Paradiso added to that, but, certainly, in terms of finding the preservative, the clinical trials for the products containing that preservative, the regulatory issues in terms of approval and, subsequently, reformulation, we're probably talking about a minimum of five years before new preservative preparations are on the market. And that may be, give or take, two or three years.

In terms of thimerosal, by either spelling, it works and has worked for these many years and one can at least have some confidence that disasters have not occurred to our knowledge from such usage, but the toxicity data are limited. And what has been presented to us by our colleagues in toxicology is that the data on methylmercury has been used in the assessment of

risks associated with ethylmercury and the toxicity profile of the two compounds should be considered to be similar so that, even though it may be a stretch that ethyl and methyl are similar, the absence of information dictates what we need to use the data about methyl at least is a starting point and surrogate for our discussions.

In terms of thimerosal, again, that it's not the amount of the preservative in each vaccine, but it's now with the burst of new product and the cumulative amount of mercury that is present that has raised the concern.

I think most important is the words "eliminate/reduce" and that the perception should be, particularly keeping in mind the timetable of years, that our goal is to achieve elimination but first reduction and that those terms always be used in a paired fashion and that the gradual changes, rather than precipitous changes, is a reality.

Finally, we talked a lot about delivering the message and I think that's an increasing part of our decision-making, and at anytime we do come to a change in

current policy, we need to anticipate the reception of that change among caretakers, physicians, health care workers, parents, consumer advocates, legislators, manufacturers, and particularly, I think, our role as a leader in these discussions throughout the world. So every action will have a reaction. I think a lot of the discussion yesterday about the action that was taken in changing the schedule of the hepatitis B vaccine from birth bears on that, making sure that that message and the reason for the change is delivered to those who are actually responsible for the change, the hospitals in altering their policies are cognizant of the reasons for the changes, that the clinics understand that any gaps that would be created -- I think Bob Down's data and the CDC data that suggest that that first immunization in the nursery is very important in subsequent vaccine utilization by selected families leads us to believe that delivering the message and the caretaker's delivering the message to the parents becomes a very critical part in decision-making.

I think Gina said it very well, that the generic issue is to become more capable, more skilled in how to communicate controversial and inconclusive data so that we maintain confidence of our public. And as long as -- the time that I've been on the Red Book and subsequently, this has been and will be a continued challenge, and I think we need all the help we can get in making sure that our decisions not only are appropriate scientifically, but they are communicated to the public in a manner that the constituency understands the reasons for the change and is accepting of those changes.

I'd like to congratulate Dr. Myers and staff for putting together a meeting that I find to have been one of the most informative and interesting programs that I've attended in a long time. So thank you very much, Marty.

(APPLAUSE)

(CONCLUSION OF WORKSHOP AT APPROXIMATELY 3:14 P.M.)

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C E R T I F I C A T E

G E O R G I A)

FULTON COUNTY)

I, Pamela T. Lennard, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that the foregoing, consisting of pages 1 through 238 (DAY TWO - VOLUME I) inclusive, was reduced to typewriting by me personally or under my supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

I further certify that I am not related to, employed by, or attorney or counsel for any parties, attorneys, or counsel involved herein; nor am I financially interested in this matter.

WITNESS MY HAND AND OFFICIAL SEAL, this 5th day of September, 1999.

Pamela T. Lennard, CCR-CVR
CCR No. B-1797

[SEAL]